American Journal of Medical Genetics 62:391–397 (1996)

Anophthalmia-Waardenburg Syndrome: A Report of Three Cases

Zuhal Suyugül, Mehmet Seven, Seniha Hacıhanefioğlu, Ayşın Kartal, Nezir Suyugül, and Asım Cenani

Genetic and Teratology Research Center (Z.S., M.S., A.K., A.C.), Department of Medical Biology and Genetics (S.H.), and Department of Ophthalmology (N.S.), Cerrahpaşa Medical Faculty, University of Istanbul, Istanbul, Turkey

We report on 2 Turkish families with children who had bilateral anophthalmia, upper and lower limb abnormalities, mental retardation and consanguineous parents. We have evaluated the 2 cases in the first family and the only case in the second as anophthalmia-Waardenburg syndrome. This is an extremely rare autosomal recessive syndrome. © 1996 Wiley-Liss, Inc.

KEY WORDS: anophthalmia, syndrome of Waardenburg, multiple congenital abnormalities, autosomal recessive inheritance, parental consanguinity

INTRODUCTION

Anophthalmia is a rare defect. It can be isolated or associated with other manifestations in syndromes. Autosomal recessive anophthalmia associated with skeletal abnormalities was described by Waardenburg [1961]. Later, Richieri-Costa et al. [1983], Pallotta and Dallapiccola [1984] and Le Merrer et al. [1988] published cases of the same syndrome. Here we present three cases born to two separate consanguineous couples.

CLINICAL REPORTS

Family 1, Patient 1

Y.E. (Fig. 1) was a 6-year-old girl, second child of consanguineous parents. Her mother and father were children of paternal uncles (Fig. 2). The child's inbreeding coefficient is F = 1/28 = 0.035. Her delivery was by cesarean at term after an uncomplicated pregnancy. There was no history of drug use, X-ray exposure, traumatic and infectious incidents, respiratory problems, convulsions, or feeding problems. Birth weight was 2,500 g, but length was unknown. Present weight and height were under the third centile. Her face was smaller than her head. She had mild frontal bossing, flat nasal bridge, closed eyelids, absence of globes on palpation, normal eyebrows and eyelashes and short palpebral fissures. Mental retardation was present. According to our observations the patient can understand actual speech but doesn't talk. She responds to love and affection.

CT scan of the orbits showed absence of globes, normal lacrimal glands, rudimentary optic nerves and extraocular tissues (Fig. 3). Cranial CT scan was normal. There was a big gap between the first and second fin-

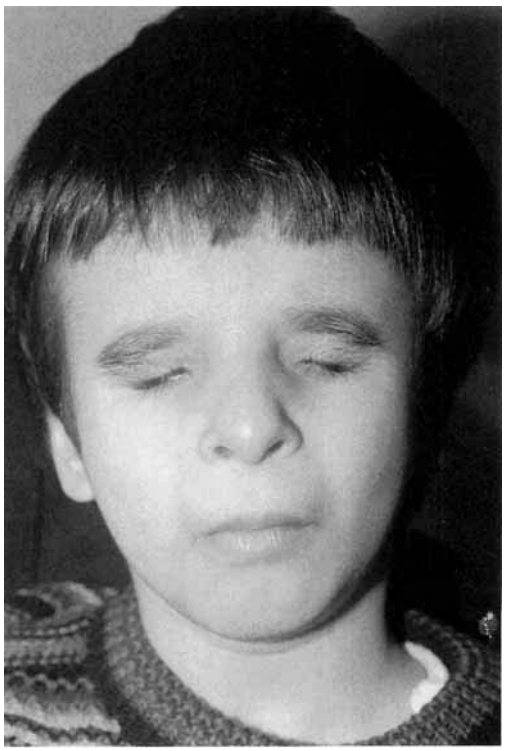

Fig. 1. Patient 1.

Received for publication May 16, 1995; revision received September 11, 1995.

Address reprint requests to Zuhal Suyugül, M.D., Ph.D., Seher Yıldızı Sok. Adak Apt. No: 16/14 Etiler/Istanbul, Turkey.

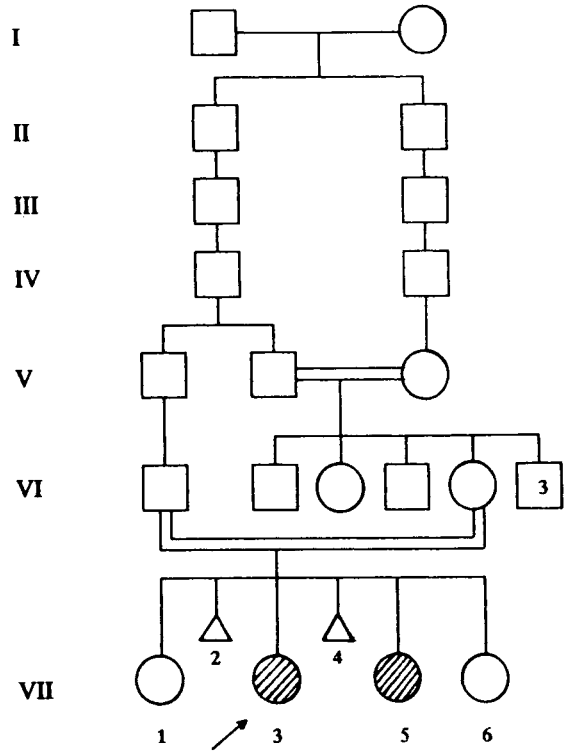

Fig. 2. Pedigree of family of patients 1 and 2.

gers of both hands. Camptodactyly, brachydactyly and clinodactyly were noted. Osseous synostosis of the 4th and 5th metacarpals was observed bilaterally (Fig. 4a,b). One toe was absent from both feet and there was cutaneous syndactyly of the second and third and osseous syndactyly of the 3rd and 4th toes (Fig. 5a,b). She also had genua valga, bowed tibiae and hypoplastic fibulae. Cardiac, abdominal and genital organs were

Fig. 3. CT scan of the orbits show absence of the globes and optic nerves.

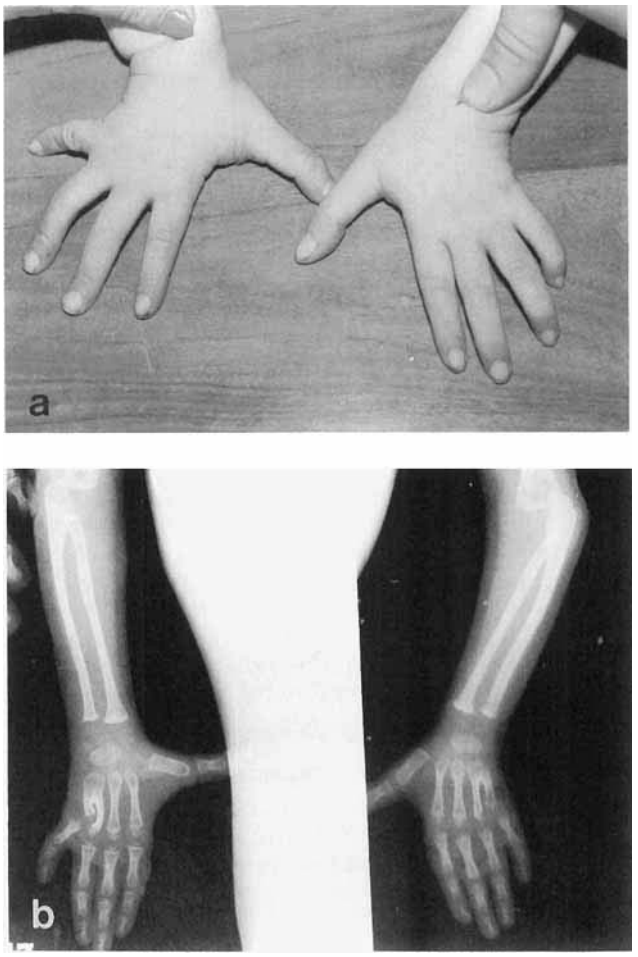

Fig. 4. **a:** The hands of patient 1. **b:** Radiological aspects of the hands of patient 1.

normal. Chromosome constitution was 46,XX. Urine and counter blood cell (CBC) were normal.

Patient 2

G.E. (Fig. 6), a 2-year-old girl, was the third child of the same family. Her manifestations were similar to those of her elder sister. There was no history of infection, trauma, drug or X-ray exposure during pregnancy. She was delivered by cesarean at term. Height and weight under the second centile, she had flat nasal bridge, closed eyelids, nonpalpable globes, short palpebral fissures, normal eyebrows and eyelashes. She had mental retardation. She can say mum, dad and mama, and expresses her feelings and responds to touch and affection better than her elder sister.

Cranial and orbital CT scans showed that both globes were absent, optic nerves and other extraocular tissues were rudimentary. Direct craniography showed hypoplasia orbits (Fig. 7). Brachydactyly, camptodactyly, and clinodactyly of both hands, synostosis of the 4th and 5th metacarpals of both hands (Fig. 8a,b) were observed. There was cutaneous syndactyly of the second and third and osseous syndactyly of the 3rd and 4th

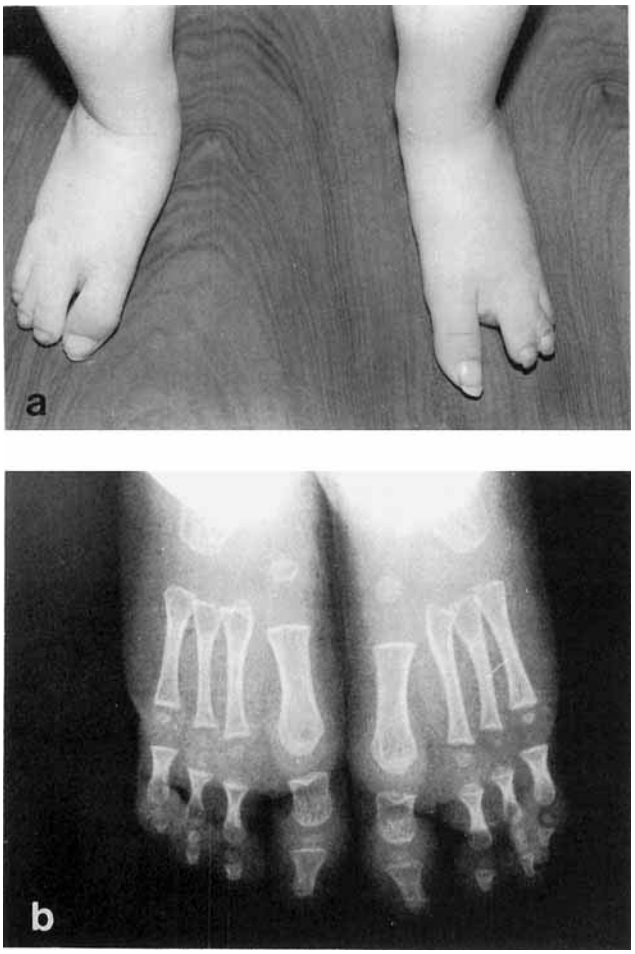

Fig. 5. **a:** The feet of patient 1. **b:** Radiological aspects of the feet of patient 1.

Fig. 6. Patient 2.

toes. One toe was absent from both feet (Fig. 9a,b), tibiae were bowed. Chromosomes (46,XX) were normal as were the other systems.

The parents of the patients whom we mentioned above consulted us for genetic counselling during the 4th pregnancy while the fetus was at 26 weeks. We determined that the development of the eyes (Fig. 9) and limbs was normal. The infant was healthy and normally developed at birth.

Family 2, Patient 1

S.A. (Fig. 10) was an 11-year-old boy of consanguineous parents (Fig. 11). The child's inbreeding coefficient is F = 1/64 = 0.015. He was the only child of the family. His delivery was normal at term, after an uncomplicated pregnancy. Birth weight and length were 3,000 g and 50 cm, respectively. His present height was below the third centile, and weight was between the 3rd and 10th centile. He had mental retardation. He can say mum, dad and express his hunger. He responds to touch and affection. He had a small face with respect to the head, prominent forehead, flat nasal bridge, closed eyelids and narrow palpebral fissures, absence of globes on palpation. Orbital CT scan showed normal optic nerves and normal extraocular tissues but absent globes. Cranial CT documented normal cerebral and cerebellar structures. He also had cutaneous syndactyly, clinodactyly and brachydactyly of both hands (Fig. 12a,b), and cutaneous syndactyly of the second and third toes of both feet, one toe was absent (Fig.

Fig. 7. CT scan of the orbis show bilateral absence of the globes and optic nerves.

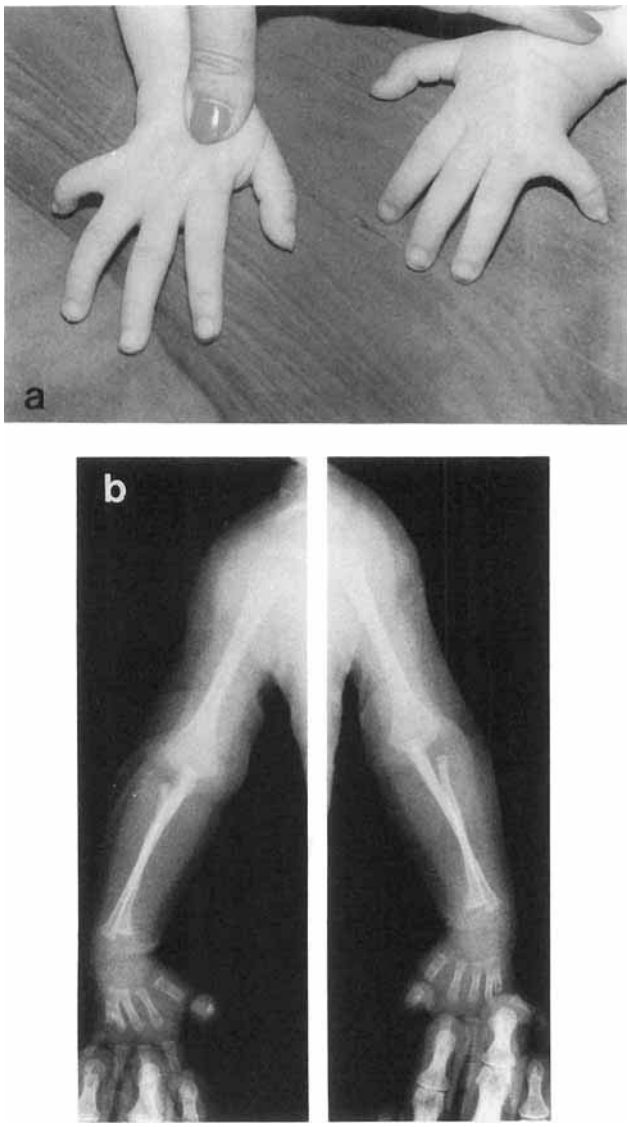

Fig. 8. **a:** The hands of patient 2. **b:** Radiological aspects of the hands of patient 2.

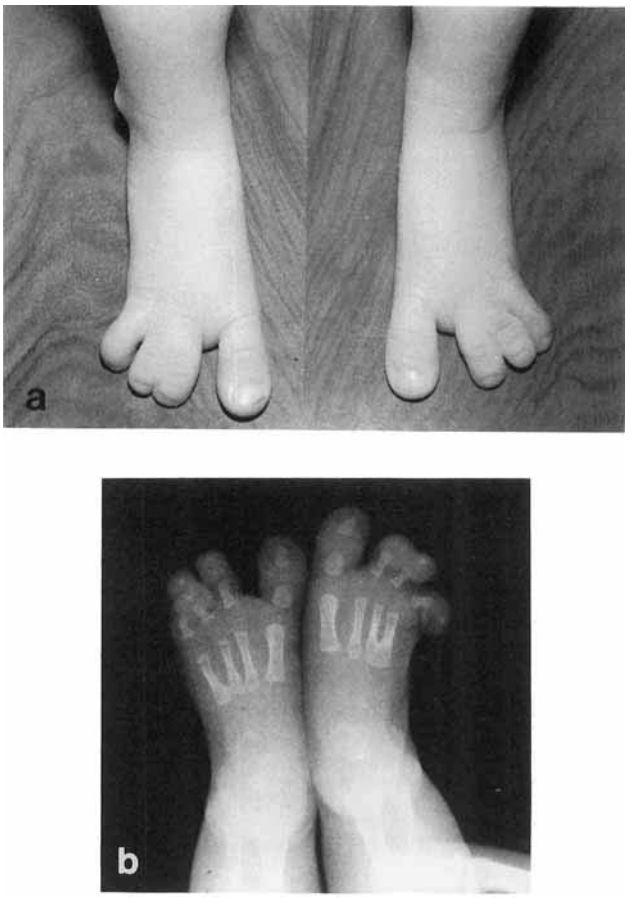

Fig. 9. **a:** The feet of patient 2. **b:** Radiological aspects of the feet of patient 2.

13a,b). Chromosomal constitution was 46,XY. Other systems were normal.

DISCUSSION

The Waardenburg anophthalmia syndrome is an autosomal recessive anophthalmia distal limb and mental defect syndrome. The condition was first described in 1950 by Waardenburg and later by Richieri-Costa et al. [1983]. This was followed by other reports. Pallotta and Dallapiccola [1984] and Le Merrer et al. [1988] published their Waardenburg syndrome-like cases but named it ophthalmo-acromelic syndrome.

The main signs of the syndrome are anophthalmia, limb abnormalities (syndactyly, oligodactyly, metacarpal/carpal synostosis, elbow and hip dislocation, bowed tibiae, absence or hypoplasia of fibulae) and mental retardation. It is an autosomal recessive trait (Table I).

Anophthalmia can be isolated or associated with other manifestations in syndromes. Genetic inheritance of isolated anophthalmia can be an autosomal

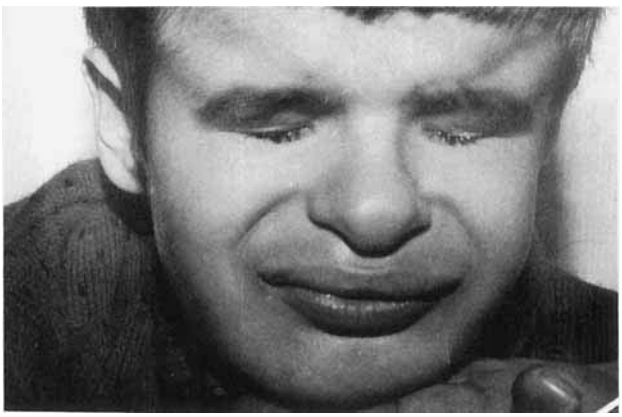

Fig. 10. Patient 3.

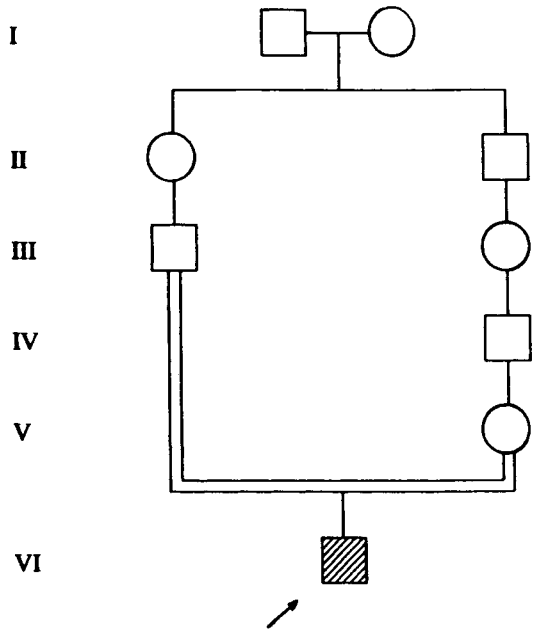

Fig. 11. Pedigree of family of patient 3.

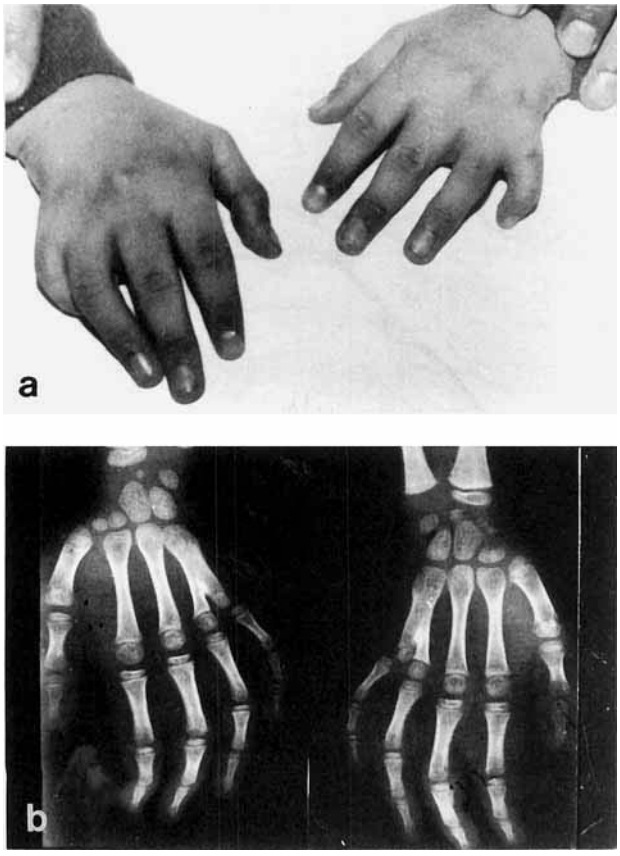

Fig. 12. **a:** The hands of patient 3. **b:** Radiological aspects of the hands of patient 3.

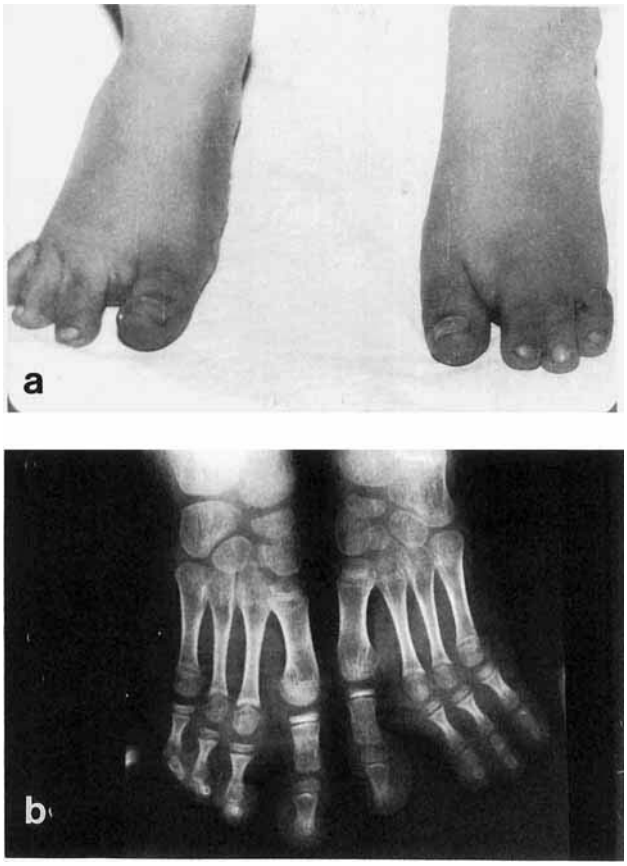

Fig. 13. **a:** The feet of patient 3. **b:** Radiological aspects of the feet of patient 3.

dominant, autosomal recessive and X-linked trait [Brunquell et al., 1984; Kohn et al., 1988; Sensi et al., 1987].

Richieri-Costa et al. diagnosed anophthalmia histopathologically after surgical exploration [Richieri-Costa et al., 1983]. Other study groups used ultrasonography or CT scan for diagnosis. Most cases had bilateral clinical anophthalmia. One patient had unilateral anophthalmia and another patient had anophthalmia of one eye and microphthalmia of the other. We used CT scan in our cases. In 3 children of our 2 families we have diagnosed clinical anophthalmia.

Another major sign of Waardenburg syndrome is distal limb anomaly. Most cases in the literature and 3 of our cases had brachydactyly, camptodactyly and osseous syndactyly of the 4th and 5th fingers. Lower distal limb abnormalities (oligodactyly, skin and/or osseous syndactyly) were also present. Bowed tibiae and ulnar hypoplasia were also reported. All of the lower limb abnormalities were present in our 3 cases.

Normally, eyes and limbs show temporal synchronization and sequential progression during embryogenesis. This morphogenetic program is under the control of more than one interacting gene. Any abnormality of one of these genes may affect these two development

TABLE I. Clinical Findings in Autosomal Recessive Anophthalmia Type Waardenburg*

	Waardenburg's cases				Richieri-Costa, Gollop and Otto cases					Our cases		
	Case 1	Family I Case 2	Case 3	Family II	Family I	Case 1	Case 2	Family II Case 3	Case 4	Family I Case 1	Case 2	Family II Case
Parental consanguinity	+	+	+	+	+	+	+	+	+	+	+	+
Sex	F[b]	F	M[c]	F	M	F	F	M	F	F	F	M
Anophthalmia L	+	+		+	+	+	+	+	+	+	+	+
R	C[a]	–	–	+	+	N	+	+	+	+	+	+
Small orbits	?	?		?	+	+				N	+	?
Narrow palpebral fissures	?	?		?	+	+						
				+	+	+						
Antimongoloid slant	?	?		?	+	+				+	+	+
Eyelashes	?	?		?	N	N				N	N	N
Eyebrows	?	?		?	N	N				N	N	N
Eyelids	?	?		?	N	N				N	N	N
Metacarpals 4 and 5 fused	+	+		?	+	+				+	+	+
Hand malformation	+	+		+	+	+	–	–	–	+	+	+
Camptodactyly	?	?		?	+	+				+	+	+
Thin palmar region	?	?		?	+	+				+	+	+
Syndactyly of fingers	?	?		+	+					+	+	+
Malformation of feet	+	+		+	+	+	–	–	–	+	+	+
Syndactyly of toes	–	–		–		+				+	+	+
Oligodactyly of toes	–	–		+	+	+				+	+	+
Clubfoot	–	–		–	+					–	–	–
Mental retardations	–	–		–	+	–	–			+	+	+
Bowed tibia										+	+	?
Hypoplastic fibulae										+	+	?

* Richieri-Costa et al. [1983].
[a] C: Colobom.
[b] F: Female.
[c] M: Male.

fields (eye and distal limbs) and cause developmental defects. The variability of the abnormalities can be explained by variable expression of the genes. This idea is somewhat reinforced when one compares the findings in our patients with embryological studies of a syndrome in the mouse [Buyse, 1990; Richieri-Costa et al., 1983].

Autosomal recessive eye and skeletal system syndromes are similar to each other. Therefore, differential diagnosis should be made very carefully. For example, clinically these cases can be distinguished from oculofacio-skeletal syndrome on the basis of absence of cerebral findings. This form of anophthalmia is clearly different from the Lenz microphthalmia syndrome which is associated with dental, urogenital and cardiac abnormalities that are not observed in this anophthalmia syndrome. The condition is also early distinguishable from the Fraser syndrome on the basis of absence of cryptophthalmia. This syndrome also is distinct from focal dermal hypoplasia.

The clinical findings of our 3 cases are typical of the Waardenburg anophthalmia syndrome, a rare disorder which is recessively inherited.

REFERENCES

Brunquell PJ, Papale JH, Horton JC et al. (1984): Sex-linked hereditary bilateral anophthalmos. Arch Ophthalmol 102:108–113.

Buyse ML (1990): "Birth Defects Encyclopedia. Center for Birth Defects Information Services USA" Massachusetts: Blackwell Scientific Publications, pp 147–148.

Kohn G, Shawwa RE, Rayyes EE (1988): Isolated clinical anophthalmia in an extensively affected Arab kindred. Clin Genet 33: 321–324.

Le Merrer M, Nessmann C, Briad ML, Maroteaux P (1988): Ophthalmo-acromelic syndrome. Ann Génét 31:226–229.

Pallotta R, Dallapiccola BA (1984): Syndrome with true anophthalmia, hand foot defects and mental retardation. Ophthal Pead Genet 4:19–23.

Richieri-Costa A, Gollop TR, Otto PG (1983): Brief clinical report: Autosomal recessive anophthalmia with multiple congenital abnormalities type Waardenburg. Am J Med Genet 14:607–615.

Sensi A, Incorvaia C, Sebastiani A, Cazolari E (1987): Clinical anophthalmos in a family. Clin Genet 32:156–159.

Waardenburg PJ (1961): Anophthalmia resp. *microphthalmia as part* of a larger syndrome. In: Waardenburg PJ, Franceschetti A, Klein D (eds). Genetics and Ophthalmology. Oxford: Blackwell Scientific Publications, pp 773–775.

Winter RM, Baraitser M (1991): "Multiple Congenital Anomalies. Part One. A Catalogue of Multiple Congenital Anomaly Syndromes. Anophthalmia Type Waardenburg (1th ed). London Chapman and Hall Medical, pp 37–38.